Remarks

The December 18, 2003 Official Action has been carefully considered. In view of the amendments submitted herewith and these remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, it is noted that a shortened statutory response period of three (3) months was set in the December 18, 2003 Official Action. The initial due date for response, therefore, was March 18, 2004. A petition for a three (3) month extension of the response period is presented with this amendment and request for reconsideration, which is being filed before the expiration of the three (3) month extension period.

As a further preliminary matter, it is noted that the requirements for restriction and election of species set forth in the immediately preceding Official Action have been maintained and made final. Applicants wish to make clear that their election of claims 1-32 and 42-49 for examination in this application is without prejudice to their right to file one or more divisional applications, as provided in 35 U.S.C. §121, directed to any and all subject matter held withdrawn from consideration in the present application.

In the December 18, 2003 Official Action, claims 17 and 18 are objected to under 37 C.F.R. §1.75(c) as allegedly being in improper form. This objection is based on an invalid premise, i.e. that claim 17 is a multiple dependent claim. It is not. As a proper dependent claim, claim 17 further limits claim 16 by

reciting that the nucleic acid referred to therein (which is the nucleic acid of claim 1) is operably linked to a promoter. In this connection, claim 17 has been amended to recite "said nucleic acid", in place of "the nucleic acid of claim 1". Thus, the objection to claim 17 based on 37 C.F.R. §1.75(c) is believed to be overcome. The same is true with respect to the objection to claim 18, which is based on the same grounds. In view of the amendment to claim 17 presented herewith, both claims 17 and 18 should be examined on the merits.

A number of additional formal objections are set forth at pages 4-5 of the December 18, 2003 Official Action. These objections are addressed and overcome by the present amendment and remarks.

Turning to the substantive aspects of the December 18, 2003 Official Action, claims 1-16, 19-32 and 42-47 stand rejected for allegedly failing to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. According to the Examiner, the specification is not enabling for nucleic acids encoding a fusion protein comprising any toxin domain fused to any heterologous binding domain that binds to a cell membrane without disrupting it.

Claims 1-16, 19-32 and 42-47 have been further rejected for allegedly failing to comply with the written specification requirement of 35 U.S.C. §112 for subject matter other than a CryIA(b) or cryI(c) toxin domain fused to RTB, because, in the Examiners view, the specification does not describe other DNA

molecules encompassed by the claims.

Claims 1-16, 19-32 and 42-47 have also been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. The specific claim terminology giving rise to this rejection is identified at pages 8-10 of the December 18, 2003 Official Action.

Claims 1-4, 12-16, 20-22, 43 and 44 have also been rejected under 35 U.S.C. §102(b) as allegedly anticipated by the disclosure of U.S. patent 5,668,255 to Murphy.

Claims 1-4, 9, 12-16, 19-23, 26, 27, 31, 32 and 43-45 have been further rejected under 35 U.S.C. §102(b) as allegedly anticipated by the disclosure of U.S. patent 5,290,914 to Wilcox et al., taken with the evidence of Crickmore et al. (Micro.Mole.Biol.Rev., 62:807-13 (1998)).

Claims 1-16, 19-23, 26, 27, 31, 32 and 42-45 have been further rejected under 35 U.S.C. §103 as allegedly unpatentable in view of the combined disclosures of the above-mentioned Wilcox et al. patent and U.S. patent 5,538,868 to Horn et al. According to the Examiner, it would have been obvious to one of ordinary skill in the art at the time the present invention was made to modify the method of using a nucleic acid encoding the pesticidal fusion between a Bt toxin and diphtheria toxin B chain to increase pest resistance in a plant, as purportedly taught by Wilcox et al., by substituting the diphtheria B chain with the ricin B chain described in Horn et al.

Claims 24, 25, 28-30, 46 and 47 have also been rejected

under 35 U.S.C. §103 as allegedly unpatentable in view of the combined disclosures of the Wilcox et al. patent, the Horn et al. patent and Gordon-Kamm et al. (Plant Cell,2:603-18 (1990)). According to the Examiner it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of using a nucleic acid encoding a pesticidal fusion between a Bt toxin and diphtheria toxin B chain to increase pest resistance in a plant, as purportedly taught by Wilcox et al. in view of Horn et al., by transforming the nucleic acid into a maize plant, as described in Gordon-Kamm et al.

The foregoing objections and rejections constitute all of the grounds set forth in the December 18, 2003 Official Action for refusing the present application.

In accordance with the present amendment, claims 1 and 13 have been amended in the same manner to recite that the binding domain is derived from a lectin. Support for this amendment is provided by the specific exemplification of sequences of ricin toxin B domain (RTB1, RTB2, RTB3) and GNA, which are representative of a binding domain that is derived from a lectin.

Claim 3 is now amended to recite CryIA(b) or CryIA(c), instead of CryIA(b) or (c).

Claims 5 and 7 have been amended so as to depend from claim 1, in view of the cancellation of claims 4 and 6, respectively, in accordance with this amendment.

Claim 9 is now amended to characterize the toxin domain

as "derived from CryIA(b) as encoded by SEQ ID NO: 1 or CryIA(c) as encoded by SEQ ID NO: 2".

Claim 10 is now amended to characterize the binding domain as "derived from RTB1 as encoded by SEQ ID NO: 3, RTB2 as encoded by SEQ ID NO: 4, or RTB3 as encoded by SEQ ID NO: 5".

Claim 12, as amended, calls for a nucleotide sequence which shares at least 90% homology with any of SEQ ID NOs: 1-11. Support for this amendment is provided in the present specification at pages 11-12, and in particular page 11, lines 33-37.

Claim 26 has been amended to refer to a plant cell rather than a host cell.

Claim 27 has been amended by deleting wording which is considered superfluous in view of the previous amendment to claim 26.

Claim 32 has been amended to call for the step of expressing a nucleic acid of claim 1 in the plant.

No new matter has been introduced into this application by reason of any of the amendments presented herewith.

For the reasons set forth below, Applicants respectfully submit that the various objections and rejections set forth in the December 18, 2003 Official Action, as summarized hereinabove, cannot be maintained in view of the present claim amendments. Those grounds of rejection are, therefore, respectfully traversed.

A. The Present Specification Provides A Fully Enabling Disclosure with Respect To The Subject Matter Of Claims 1-16, 19-32 and 42-47, As Now Amended

Initially, it is noted that although the Examiner asserts that the specification is not enabling for nucleic acids encoding a fusion protein comprising any toxin domain fused to any heterologous binding domain, the Office Action does not provide any reasoning to substantiate the rejection. The rejection should be withdrawn unless the Examiner can reasonably back up the rejection. As stated in In re Marzocchi,439 F.2d 220, 223 169 U.S.P.Q. 367, 369 370 (CCPA 1971):

"(I)t is incumbent upon the Office to explain why it doubts the truth of the enabling assertions and to back up it's view with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the Applicant to go to the trouble and expense of supporting his PRESUMPTIVELY ACCURATE disclosure."

In the interests of not unduly delaying prosecution, however, claims 1 and 13 are amended to recite that the binding domain is derived from a lectin. As a result of this amendment the sufficiency of enablement provided by the present specification is beyond question.

As noted by the Examiner, the specification is enabling for nucleic acids encoding a fusion protein comprising a CryIAb or CryIAc toxin domain fused to the ricin

binding domain. The specification demonstrates that fusion proteins comprising CryIAb or CryIAc as the toxin domain and ricin toxin B (RTB1, RTB2 and RTB3) as the binding domain have pesticidal activity (e.g., see Examples 4 and 6 in the specification). Details of how the nucleic acids were made are provided in Examples 1-3. Based on the teaching in the specification, the skilled person can readily construct nucleic acids comprising toxins and/or lectins other than those specifically used in the disclosed experiments. The specification is also enabling for nucleic acids encoding fusion proteins comprising other toxins and other binding domains, as explained below.

1- Enablement for toxins other than CryI(a) and CryI(b)

The application contains experimental details and results illustrating the mechanism of action of the lectin component of the molecule with one class of toxins, including two different Bt toxins. These data demonstrate that pesticidal toxins comprising a lectin and a toxin can be successfully made and used.

What the Applicants have shown is a principle of action. They have shown that a lectin can be used to enhance the binding of a toxin domain to cells, thereby increasing its effectiveness as a toxin.

Based on the experimental data, and as disclosed in the specification, the skilled person knows that other pesticidal toxins can also be used in the same way.

Consequently, if a molecule has insecticidal activity, fusing it to a lectin will enhance its activity along the same lines as the Applicants' specific examples with Bt.

The specification makes clear that any pesticidal toxin can be used in the invention, in the same manner as the specifically exemplified cry toxins. Examples of other toxins are protease inhibitors from cowpea and soybean (see page 1, lines 11-21). There is no reason to doubt that pesticidal fusions made using these toxins could be made and used, and every reason to believe that such fusions would be effective pesticide.

Making the required nucleic acid constructs places no undue burden on the skilled person, as straightforward molecular biology techniques are well known and widely used for such purpose.

Accordingly, limitation to the particular class of toxins used in the examples is not commensurate with the Applicants' contribution to the art and would unduly restrict the claim scope. The allowed claims should be of sufficient scope to adequately protect Applicants' invention. In re Goffe, 191 U.S.P.Q. 429,431 (CCPA 1976)

2 - Enablement for all lectins

Lectins are a class of proteins that bind to sugar residues. In the present invention a lectin is fused to a toxin, and the lectin binds to cell membranes. As noted above, the Applicants have demonstrated a general principle,

whereby fusion of a lectin to a toxin domain increases the toxin's activity against the target cells.

In the specification, the experiments use RTB (RTB1, RTB2 and RTB3), and these RTB domains are used in fusion proteins with two different Bt toxins. The examples show that fusion proteins comprising a toxin domain and RTB as a binding domain have pesticidal activity (e.g. Examples 4 and 6 in the specification). Activity of a second lectin "GNA" is also shown in the specification. Example 7 shows that GNA binds to insect gut extracts. Moreover, this example shows that a fusion of GNA and a toxin increases binding of the toxin to insect gut, extending the range of molecular interactions available to the toxin. This indicates that the lectin GNA enhances toxin binding and potentially broadens the spectrum of the toxin's pesticidal activity.

Thus, the specification demonstrates successful use of pesticidal fusions with a plurality of different lectins (RTB1, RTB2, RTB3, GNA). Other lectins can be substituted and used in the present invention, and would have the same effect because they function in the same way i.e. they bind sugar residues and thus enhance contact between the attached toxin and the target cells. Therefore, the present invention is not limited to particular lectins but can legitimately be generalized to all lectins.

In summary, the Applicants have shown a plurality of cry toxins and a plurality of lectins, and have thus

demonstrated that the full scope of the claimed subject matter is enabled.

3 - Enablement for homologous variants and modification of the toxin or binding domain

The Examiner asserts that the specification fails to provide guidance for homologous variants of SEQ ID NO: 6 or for modification of the toxin or binding domain.

Both (i) the toxin domain and (ii) the binding domain are proteins, and it is well known in the art of genetics and protein science that nucleic acid and protein amino acid sequences can be varied while retaining function. In general, the entire sequence of a protein is not necessary for its activity. Virtually all proteins have regions present for different reasons, and in the present invention Applicants are concerned only with parts that contribute to (i) toxin activity and (ii) binding. The skilled person understands and expects that changes can be made to specified sequences while retaining function, and methods of making modifications to sequences are routine in the art. Methods of making variant sequences, and possible reasons why the skilled person would do so, are described in the specification on page 11 line 34 to page 15 line 23.

The skilled person is aware that a nucleic acid coding sequence can be mutated without function being lost. Mutations in a coding sequence may not affect the sequence of the encoded polypeptide, because of the degeneracy of the

genetic code. Even where mutations do result in addition, deletion or substitution of one or more amino acid residues, the polypeptide's function is normally maintained, at least to some degree. In many cases, function is completely unaffected, because many amino acid locations in a protein are non-critical for its function. The skilled person is familiar with the types of mutations that can be made, and is readily able to generate mutations in the sequence where the expression product manifests pesticidal activity.

Furthermore, claims to variant sequences, and to methods of making variant proteins, are commonly allowed by the USPTO and other patent offices.

The fact that the skilled person can make fusions comprising variants of sequences according to the present invention is illustrated by the fact that Applicants have now shown that toxic activity of the fusions is maintained even when part of the RTB domain is deleted. Applicants experimented with a series of deletions of RTB, and found that longer RTB portions had higher toxicity and a broader pesticidal spectrum. However, it is clear that when part of the RTB domain is deleted, the fusion polypeptides are still functional.

The Examiner cites papers by Lazar et al. and Hill and Preiss, to make the point that in some instances conservative substitutions can affect protein activity. However, these examples are exceptions to the general

principle, explained above (and were no doubt published for that reason), that changes can be made to a coding sequence without substantially affecting the protein activity. However, enablement only requires that the skilled person can make and use the invention, without undue experimentation (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is "undue" (Id. at 736 37, 8 USPQ2d at 1404), and the mere fact that some experimentation is needed does not mean that there is undue burden on the skilled person. It is inherent in the art of molecular biology that mutations can have unpredictable effects, and that therefore some experimentation may be required, but the skilled person faces no undue burden in generating functional variants of a known sequence owing to the well-established principles of molecular biology and the ready availability of the necessary techniques.

It is also noted that there would not be any undue burden on the skilled person to introduce any of the claimed nucleic acid constructs into host cells, nor to produce transgenic plants from transformed plant host cells. The relevant protocols and techniques are well known in the art and the skilled person can easily transform cells with the constructs of the invention, regardless of the sequence or origin of the nucleic acids.

Accordingly, the claimed invention is enabled throughout the full scope of the claims. That being the case, the rejection of claims 1-16, 19-32 and 42-47 under 35 U.S.C. §112, first paragraph for inadequate enablement is untenable and should be withdrawn.

B. Claims 1-16, 19-32 And 42-47, As Currently Amended, Fully Comply With The Written Specification Requirement Of 35 U.S.C. §112, First Paragraph

The relevant inquiry in determining compliance with the written specification requirement of 35 U.S.C. §112, first paragraph, is whether the originally filed specification reasonably conveys to a person having ordinary skill in the art that Applicant had possession of the claimed subject matter. In re Kaslow, 217 U.S.P.Q. 1089 (Fed. Cir. 1983).

Furthermore, the Examiner has the initial burden of presenting evidence or reasons why a person of skill in the art would not recognize in Applicants' specification disclosure a specification of the invention defined by the claims. Ex parte Sorenson, 3 U.S.P.Q.2d 1462 (Bd. Pat. App. 1987).

The lack of written specification rejection cannot be maintained with respect to Applicant's claim as currently amended, because the claims now specify that the binding domain is derived from a lectin. The present claims thus more closely correspond to the actual fusion proteins specifically used in the experiments described in the specification.

Applicants have specifically exemplified and disclosed sequences of ricin toxin B domain (RTB1, RTB2, RTB3) and GNA, which are representative of a binding domain that is derived from a lectin. Applicants have also specifically exemplified and disclosed sequences of CryIAb and CryIAc, which are representative of toxin domains. Other lectin and toxin sequences are known in the art and can readily be selected by the skilled person and used in the present invention. The specification states that any toxin and any lectin can be used. Examples of other toxins are also explicitly given (see page 1 lines 11-21, referring to protease inhibitors from cowpea and soybean). There can be no doubt therefore that, at the time of filing, Applicants were in possession of the genus claimed.

The Guidelines for Examination of Patent Applications Under the 35 USC 112(1) "Written Specification" Requirement (Federal Register, 2001) state that:

"For each claim drawn to a genus:

The written specification requirement for a claimed genus may be satisfied through sufficient specification of a representative number of species by actual reduction to practice (see (1)(a), above), reduction to drawings (see 1)(b), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and

structure, or by a combination of such identifying characteristics, sufficient to show the Applicant was in possession of the claimed genus (see 1)(c), above).

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. On the other hand, there may be situations where one species adequately supports a genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written specification of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. Specification of a representative number of species does not require the specification to be of such specificity that it would provide individual support for each species that the genus embraces. If a representative number of adequately described species are not disclosed for a genus, the claim to that genus must be rejected as lacking adequate written specification under 35 U.S.C. 112."

In the present claims, the genus is now restricted to toxins and lectins rather than any binding domain capable of binding non-specifically to a cell membrane without disrupting that membrane. As explained above , in refuting the inadequate enablement rejection, the art of molecular biology is well established and the skilled person can readily generate nucleic acid constructs comprising any toxin and any lectin. Applicants' disclosure of specifically exemplified toxins and a lectin convey to the skilled person that the Applicant was in possession of the claimed genus in view of the species disclosed.

The Examiners comment concerning "any toxin domain" and "any heterologous binding domain" in the paragraph bridging pages 7-8 of the office action is not understood. The specification cannot reasonably be expected to individually describe <u>every</u> possible embodiment since that would be an impossibility. It does, however, describe a representative number of species which are sufficient to establish that the Applicants were in possession of the claimed subject matter as of the filing date of this application.

For all of the foregoing reasons, it is clear that in the present case, the Examiner has filed to satisfy the PTO's burden of proof with respect to the lack of written specification requirement rejection, as applied to the subject matter of claims 1-16, 19-32 and 42-47, as currently amended.

Accordingly, this ground of rejection cannot be maintained with respect to the amended claims.

C. Claims 1-16, 19-32 And 42-47 Satisfy The Definiteness Requirement of 35 U.S.C. §112, Second Paragraph

The relevant inquiry in determining compliance with the definiteness requirement of 35 U.S.C. §112, second paragraph, is whether the claim in questions sets out and circumscribes a particular area with a sufficient degree of precision and particularity, such that the metes and bounds of the claimed invention are reasonably clear. In re Moore, 169 U.S.P.Q. 236 (C.C.P.A. 1971).

The definiteness of claim language may not be analyzed in the abstract, but must be considered in light of the supporting specification, with the language in question being accorded the broadest reasonable interpretation consistent with its ordinary usage in the art. In re Morris, 44 U.S.P.Q.2d 1023,1027 (Fed. Cir. 1997). Se also Ex parte Cole, 223 U.S.P.Q. 94 (Bd. Apps. 1983) (claims are addressed to the person of average skill in a particular art; compliance with §112 must be adjudged from that perspective, not a in a vacuum).

Furthermore, it has long been held that the initial burden of establishing a failure to comply with 35 U.S.C. §112, second paragraph, rests upon the Examiner. In rejecting a claim for alleged indefiniteness, therefore, it is incumbent upon the Examiner to establish that one having ordinary skill

in the art would not have been able to ascertain the scope of protection defined by the claim when read in light of the supporting specification. Ex parte Cordova, 10 U.S.P.Q.2d 1949, 1952 (PTO B.P.A.I. 1988).

When the appropriate procedural approach is followed in assessing the claim terminology at issue, in accordance with the above-noted authorities, it is apparent that Applicants have satisfied the definiteness requirement of §112, second paragraph, with respect to the subject matter of claims 1-16, 19-32 and 42-47.

Applicants respectfully submit that the specific claim terminology in question is both clear and definite for the following reasons:

Toxin - The nature of the term "toxin" is clear to the skilled person. The skilled person would also recognize what is meant by "pesticidal" or "toxic to pests". For instance in the context of a plant, organisms that damage and/or feed on the plant, such as sap-sucking insects, would generally be regarded as pests, and the pesticidal fusions would be toxic to such pests.

Non-specifically - The specification in the paragraph bridging pages 6-7 of the specification explains that "non-specifically" in this context means not requiring a particular, specific, receptor.

Derived - This term is clear and is used in its ordinary sense in claim 2. The skilled person would know

whether or not a toxin is derived from a toxin, and whether or not it is derived from a lectin.

Degeneratively equivalent thereto - The degeneracy refers to the degeneracy of the genetic code. In other words, the claims are directed to any sequence that encodes the specified amino acid sequence, taking into account the fact a given amino acid can be encoded by more than one possible codon. Claims 9 and 10 as now amended are both clear and definite.

Homologous variant - Claim 12 is amended to state that the sequence shares at least 90% homology with any one SEQ ID NOs: 1 to 11. The term "homologous variant", which gave rise to this aspect of the rejection, is deleted. Basis for the amendment is on pages 11-12, especially page 11 lines 33-37. The specification also specifies how % homology can be determined, e.g. see page 11 lines 24-30.

Combining - The skilled person knows how to combine the specified nucleic acids to produce the nucleic acid of the claim. It is not a requirement for a claim to specify steps or methods that are obvious to the skilled person in context.

Addition, insertion...the nucleic acid - The method of claim 14 depends from claim 13, which includes the functional limitations that the fusion must be pesticidal and that the binding domain must be capable of binding non-specifically to a cell membrane without disrupting it. Thus, the sequence is mutated but not to the extent that it no

longer fulfils the required function. The claim is clear to the skilled person because, as noted above, the skilled person knows how to make changes in a nucleic acid sequence without the activity of the encoded protein being lost.

Modification - This term is amended to "modifying" for consistency with claim 14.

Includes - This term is amended to "comprises" as an inclusive meaning is intended.

Containing - It has long been recognized that this term is synonymous with "comprising", i.e. an open-ended term Price v. Vandenberg v. Bailey, 174 U.S.P.Q. 42 (B.O.P.I. 1971); Ex parte Glycofrides, 63 U.S.P.Q. 242 (Bd. Apps. 1994). Its use in claims 21, 27 and 43 is thus both clear and definite.

Said transformed host cell - This term is amended to "transformed plant cell".

Causing or allowing expression - This rejection should apply only to claim 32, not claim 26. The Examiner states that no inducible promoter is included in the recombinant vector. This is not necessarily the case. Claim 32 does not require the presence of an inducible promoter, but nor does it exclude it. The skilled person would know what is meant by "causing or allowing expression", and the language is clear in its context. In the interest of expediting prosecution of this application, however, claim 32 is amended to call for expressing a nucleic acid.

Selfed or hybrid progeny - The progeny are progeny of the plant of claim 27, which is obtainable by the process of claim 26, in which process the nucleic acid from the vector is introduced into the genome through recombination between the vector and the cell genome. Thus, the genomes of the progeny would contain the nucleic acid. The nature of the plant in claim 28 is thus clear to the person skilled in the art.

In summary, Applicant's position with respect to the indefiniteness rejection of claims 1-16, 19-32 and 42-47 based on 35 U.S.C. §112, second paragraph, is that any person of ordinary skill in the art, having Applicants' disclosure and claims before him or her, would be apprised to a reasonable degree of certainty as to the exact subject matter encompassed within claims 1-16, 19-32 ad 42-47. Northing more is required under 35 U.S.C. §112, second paragraph.

For all of the foregoing reasons, it is clear that in the present case, the Examiner has failed to satisfy the PTO's burden of proof with respect to the §112, second paragraph, rejection of claims 1-16, 19-32 and 42-47 as set forth in the December 18, 2003 Official Action. Accordingly, this ground of rejection is improper and should be withdrawn.

D. The Prior Art Cited In Support Of The §102(b) Rejections Of Claims 1-4, 9, 12-16, 19-23, 26, 27, 31, 32 And 43-45 Fails To Constitute Evidence Of Lack Of Novelty

Rejections under 35 U.S.C. §102 are proper only when

the claimed subject matter is identically disclosed or described in the reference cited as evidence of lack of novelty. In re Arkley, 172 U.S.P.Q. 524 (C.C.P.A. 1972). Applying this rule of law to the present case, the 35 U.S.C. §102(b) rejections of claims 1-4, 12-16, 20-22, 43 and 44 based on Murphy, and of claims 1-4, 9, 12-16, 19-23, 26, 27, 31, 32 and 43-45 based on Wilcox et al. are improper because the subject matter of those claims is nowhere identically disclosed or described in the cited references.

1. The Deficiencies in the Disclosure of Murphy

The Murphy patent generally concerns fusions of (i) a cell-binding portion, (ii) a membrane translocation domain, and (iii) a chemical to be introduced to a cell. The fusions provide a system of delivering a toxin/tracing agent/other chemical into target cells, based in principle on the bind-translocate mechanism by which diptheria toxin (DT) enters cells.

An example of the cell-binding portion is the binding domain of DT (see column 5, lines 1-30). DT is also used as the translocation domain, and a separate binding cell portion may then be used, such as IL-2 (for binding the IL-2 receptor on target lymphocytes).

Pesticidal fusions according to the present invention differ from those disclosed in Murphy in several respects.

Firstly, the binding portions of the Murphy fusions

are not lectins and do not bind "non-specifically" to cell membranes. As noted above, in the present application "non-specifically" means not requiring a particular, specific, receptor (specification, paragraph bridging pages 6-7). In Murphy, the cell-binding portion is referred to as a "ligand" (see col 2 lines 59-62), and the examples used in Murphy do bind specifically to membrane proteins. For instance, in column 3 lines 17-24, the ligand can be a hormone (which would bind to a specific hormone receptor), an antigen-binding singe-chain analog of a monoclonal antibody (which would bind to a specific antigen epitope), or a polypeptide toxin (which would bind to a receptor protein on the cell surface). None of these example ligands is a lectin, and therefore does not anticipate the present claims.

The Murphy patent deals exclusively with hybrid molecules designed for human health applications. As noted, the hybrid molecules described and claimed in the Murphy application comprise one component able to bind to a target cell and the second component is able to translocate in the cell. In Murphy, the binding and translocation domains generally have biological activity in terms of actually killing the cell. Thus, in addition to these molecules not being lectins, the gist of the present invention is clearly very different from what is claimed in Murphy. In the insecticidal fusions presently claimed the binding part of the molecule (i.e. the lectin) is **non-toxic** (it is well known that

lectins are not toxic). This is very different from what is described and claimed in Murphy. Looking at the embodiments in Murphy, the two components of the specific hybrid molecules they describe are both toxic, for example the fusion Cholera toxin A-Diphteria toxin B-IL2.

Even where the Murphy patent mentions ricin, this should not be confused with the totally different use of ricin in the present invention. Murphy uses ricin chain A, whereas the present Applicants used the ricin B chain (RTB). The A chain of ricin is highly toxic; the B chain is a non-toxic lectin. In Murphy, ricin chain A is fused to this Diphteria toxin B/IL2 to create the hybrid toxin molecule. By contrast, the present Applicants took advantage of the binding properties of the ricin B chain to enhance insecticidal activity of a conventional insecticidal protein, such as Bt.

On page 10, paragraph 11 of the Official Action, the Examiner asserts that the ricin toxin A fragments used in Murphy are "derived" from a Bt CryIA(b) or (c) toxin and that the nucleic acid is a "homologous variant" of SEQ ID NO: 6. This assertion is clearly unfounded as the toxin fragments in Murphy are not derived from a Bt Cry toxin and are not variants of SEQ ID NO: 6.

2. The Deficiencies in the Disclosure of Wilcox et al. with Evidence of Crickmore et al.

The Examiner's reliance on Wilcox et al. as evidence of lack of novelty in this case is clearly misplaced, as the

disclosure of Wilcox et al. can be seen as essentially the opposite of what present Applicants have done.

Wilcox et al. describes fusions between a Bt toxin and a cytotoxic agent. In Wilcox et al., the Bt toxin is used as a targeting, cell-binding agent to direct the cytotoxic agent to a host target (see col 1 lines 39-55). In column 1, line 46 of Wilcox et al., it is stated that the cytotoxic agent is an ADP-ribosylating enzyme and this is exemplified by using Diptheria toxin. The binding domain is the gene encoding the insect gut epithelial cell recognition portion of the Bt HD-73 gene, not the Bt toxic domain. Thus, in Wilcox et al. the Bt toxin is used as a binding domain, whereas in the present invention Bt is used as a toxin.

This can be shown figuratively:

WILCOX FUSIONS:

Binding domain Bt	**Translocation domain**	**Toxin domain** ADP-ribosylating enzyme
		(e.g. DTA, Ricin A)

PRESENT INVENTION:

Binding domain	**Toxin domain**
lectin (e.g. RTB, GNA)	pestidical toxin (e.g. Bt)

The Bt binding domain is not a lectin. Instead, Bt binds specifically to insect cells. Therefore, Wilcox et al. does not disclose a fusion between a lectin and a toxin. The

binding mechanism of the Wilcox et al. fusions are thus very different from those of the present invention, and the teaching of Wilcox et al. in no way anticipates or renders obvious the presently claimed subject matter.

The Examiner contends (page 11, paragraph 12) that Wilcox et al describes fusions between Bt toxins and diptheria toxin B chain. A careful review reveals, however, that such fusions are not shown in Wilcox et al. Col 1 lines 39-55 of Wilcox et al. indicate that the Bt toxin replaces the binding portion of the DTB chain, the result of which is a fusion between DTA and Bt toxin. This is also shown in Example 3.

The Bt in Wilcox et al. fusions serves as a binding domain to allow the diptheria toxin to kill the cells. This is the reverse of what the present Applicants have done. Rather than rendering the present invention obvious, in fact it makes the Applicants' results even more surprising!

The disclosure of Crickmore et al. fails to compensate for the patentable difference noted above between the present invention and the disclosure of Wilcox et al.

Inasmuch as neither Murphy nor Wilcox et al. identically disclose or describe all of the claim recitation of Applicants' claims 1-4, 9, 12-16, 19-23, 26, 27, 31, 32 and 43-45, as the case may be, the §102(b) rejections of such claims based on those two references is untenable and should be withdrawn.

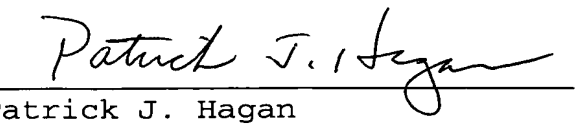
E. The Combined Disclosures Of Wilcox et al., Horn et al. and Gordon-Kamm et al. Fail To Render Obvious The Subject Matter of Applicants' Claims 1-16, 19-32 and 42-47

Regarding the obviousness rejection based on Wilcox et al in view of Horn et al. (claims 1-16, 19-23, 26, 27, 31, 32 and 42-45) and further in view of Gordon-Kamm et al. (claims 24, 25, 28-30, 46 and 47), the Examiner's positions in this regard are untenable for at least the same reasons previously discussed with respect to the impropriety of the §102 rejection of claims 1-4, 9, 12-16, 19-23, 26, 27, 31, 32 and 43-45 based primarily on Wilcox et al. Since Horn et al. and Gordon-Kamm et al., considered singularly or together, fail to compensate for the fundamental deficiencies noted above in the disclosure of Wilcox et al., the rejection of claims 1-16, 19-32 and 42-47 based on Wilcox et al. and in view of Horn et al. further in view of Gordon-Kamm et al. is likewise improper and should therefore be withdrawn.

In view of the amendments presented herewith and the foregoing remarks, it is respectfully urged that the objections and rejections set forth in the December 18, 2003

Official Action be withdrawn and that this application be passed to issue, and such action is earnestly solicited.

Respectfully submitted,
DANN, DORFMAN, HERRELL and SKILLMAN



Patrick J. Hagan
Reg. No. 27,643
Attorney for Applicants

PJH:cmb